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Published in:
Journal of Rehabilitation Medicine

DOI:
10.2340/16501977-1011

J Rehabil Med 2012; 44: 642–647

ORIGINAL REPORT

PREDICTION MODELS AND DEVELOPMENT OF AN EASY TO USE OPEN-ACCESS TOOL FOR MEASURING LUNG FUNCTION OF INDIVIDUALS WITH MOTOR COMPLETE SPINAL CORD INJURY

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Objective: **To develop statistical models to predict lung function and respiratory muscle strength from personal and lesion characteristics of individuals with motor complete spinal cord injury.**
Design: **Cross-sectional, multi-centre cohort study.**
Subjects: **A total of 440 individuals with traumatic, motor complete spinal cord injury, time post-injury ≥6 months, lesion level C4–T12, underwent measurements of lung function and respiratory muscle strength.**
Methods: **Prediction models for lung volumes and peak inspiratory and expiratory muscle strength were calculated. Using multi-level regression models, the effects of personal characteristics (gender, age, height, body mass) and lesion characteristics (time post-injury and lesion level) were determined.**
Results: **Positive predictors of lung function parameters were: male gender, younger age, greater height, greater body mass and lower lesion level. For maximal inspiratory muscle strength, male gender, younger age, greater body mass and lower lesion level were significant positive predictors, whereas for maximal expiratory muscle strength, male gender, younger age, longer time post-injury and lower lesion level were positive influencing parameters.**
Conclusion: **In contrast to predictive models for able-bodied individuals, lung function parameters of persons with spinal cord injury are influenced by body mass and lesion level. Maximal expiratory muscle strength improves with longer time post-injury.**

Key words: regression analysis; reference values; paraplegia; respiratory function tests; quadriplegia.

J Rehabil Med 2012; 44: 642–647

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Submitted November 24, 2011; accepted April 2, 2012

INTRODUCTION

Spinal cord injury (SCI) causes lesion-dependent loss of respiratory muscle innervation, which leads to impairments in respiratory muscle function and, as a consequence, to reduced respiratory muscle strength and lung volume (1). Respiratory impairment in persons with SCI may cause various types of respiratory complications, such as pneumonia, atelectasis, pleural effusions, sleep-disordered breathing or symptoms such as dyspnoea (2). Respiratory complications are still the major cause of death in persons with SCI (3). Even though the occurrence of respiratory complications during the first 2 years after injury has decreased substantially over the last 30 years, there has been no improvement thereafter, i.e. in the chronic stage of SCI (4).

Causes of respiratory complications are often multi-factorial and appear to be associated with low respiratory function (5, 6) and changes in breathing mechanics (7). With increasing time post-injury, the elastic properties of the thorax decrease, leading to impairments in lung function and respiratory muscle pressure generation capacity (8, 9). Nevertheless, individuals with tetraplegia are also able to train their remaining respiratory muscles, such as the *m. pectoralis* (10), which is used to generate expiratory pressures, or the scalene muscles, which help to elevate the ribcage and therefore increase inspiratory capacity (11). Thus, even in patients with the same lesion level there might be substantial variability in parameters of respiratory function. Detailed knowledge of additional factors determining lung function and respiratory muscle strength in persons with SCI is therefore needed. There is currently only limited knowledge of the parameters influencing lung function and respiratory muscle strength, gained from cohort studies of up to 200 individuals, mainly limited to lung function measurements in chronic SCI at around 15–20 years post-injury (12, 13). To our knowledge, there are no studies examining the parameters influencing respiratory muscle strength in persons with SCI. The primary aim of the present study was to close this gap by investigating a large sample ($n = 440$) of individuals with motor complete SCI in order to improve our basic knowledge of the determinants of lung function and respiratory muscle strength in these individuals.

The second aim of this study was to develop an easy to use calculator on an open-access web page in order to generate

 doi: 10.2340/16501977-1011
 ISSN 1650-1977

reference values for lung function and respiratory muscle strength of individuals with motor complete SCI. The calculator is based on regression equations from the present study and is intended to help clinicians improve their respiratory care management of individuals with SCI.

MATERIAL AND METHODS

Participants

Study participants were recruited from 9 SCI rehabilitation centres: 8 in the Netherlands and 1 in Switzerland. Inclusion criteria were: 18 years or older, and a motor complete SCI (American Spinal Injury Association Impairment Scale (AIS) A or B) with a lesion level between C4 and T12 and time post-injury (TPI) ≥ 6 months. Potential participants were excluded if they had one or more of the following diseases: unstable chronic obstructive pulmonary disease, severe atelectasis, lung emphysema with oxygen-dependency or a history of pneumothorax. Individuals were also excluded if they had a progressive disease or psychiatric diagnosis. Level and completeness of injury were determined using the AIS (14). All other personal data, such as gender, age and height, were recorded by the research assistant before each measurement. Body mass was measured on a wheelchair scale, after each measurement, once with the individual in the wheelchair and once without, in order to calculate the body mass of the individual without the wheelchair. Smokers were not excluded from the study in all 9 centres and smoking data (smoker, ex-smoker, non-smoker, as well as pack-years for smokers) was assessed in the Dutch centres only.

The local medical ethics committees approved all tests and protocols. The tests were conducted by 9 trained paramedic research assistants who worked in the participating rehabilitation centres. All research assistants received extensive training in how to conduct the tests. Personal and lesion characteristics were collected from questionnaire data and medical records of the respective clinics.

Lung function measurements

Lung function parameters were measured with the individual in a sitting posture in their own wheelchair using an Oxycon Delta (Oxycon Delta, Jaeger, Hoechberg, Germany) in the Dutch centres and a body plethysmograph (Master Screen Body, Jaeger, Hoechberg, Germany) in the Swiss centre. The devices were calibrated before each test. Lung function measurements were performed according to a standardized protocol (15) and consisted of forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1) and peak expiratory flow (PEF) measurements. Participants breathed through a mouthpiece while wearing a nose clip. Each measurement was performed until 3 acceptable measurements, with 2 measurements within 5%, were registered. The higher value of these 2 measurements of each parameter was used for further analysis.

Respiratory muscle strength tests

Peak inspiratory and expiratory muscle strength (Pi_{max}, Pe_{max}) were measured using an electronic manometer (Threshold Meter (self-made), Department of Physiology, Radboud University Medical Center, Nijmegen, The Netherlands) in the Dutch centres and a comparable device (MicroRPM, Care Fusion, Hoechberg, Germany) in the Swiss centre. The manometer was calibrated before each measurement and connected to a personal computer for recording the data. Individuals were in a sitting position, wearing a nose clip and breathing through a mouthpiece with a small leak to prevent glottis closure. Pi_{max} was measured from the residual volume and Pe_{max} was measured from the total lung capacity. Maximum pressures had to be maintained for at least 1 s. Individuals repeated each manoeuvre at least 3 times until 2 measurements were recorded within 5%. The highest plateau pressures (1 s) of these 2 Pi_{max} and Pe_{max} measurements were used for analysis.

Statistical analysis

Descriptive statistics (median and 2.5–97.5 percentiles) for personal and lesion characteristics were calculated for each parameter. Values were calculated separately for 4 different lesion groups: individuals with a high tetraplegia (HT), lesion level C4–C5; individuals with a low tetraplegia (LT), lesion level C6–C8; individuals with a high paraplegia (HP), lesion level T1–T6; and individuals with a low paraplegia (LP), lesion level T7–T12.

The multi-level modelling program MLwin (MLwin, version 1.1; Center for Multilevel Modelling, Institute for Education, London, UK) (16, 17) was used to determine the relationship of personal and lesion characteristics with lung function and respiratory muscle strength. Outcome variables were FVC, FEV_1, PEF, Pi_{max} and Pe_{max}. The hierarchy in the data was as follows: individual participants (level 1) who were grouped in the rehabilitation centres (level 2). In order to calculate the influence of the lesion level, 3 dummies were used and LT was determined as reference group. Further factors potentially influencing lung function and respiratory muscle strength, such as gender (male = 1, female = 0), age (years), height (m), body mass (kg) and TPI (years), as well as the interaction of lesion level and age were added one by one to a basic univariate multilevel regression model. Independent variables with p-values < 0.1 were included in a subsequent multivariate model. Model fit was assessed with the –2 Log likelihood for the models. A backward selection procedure was then carried out, excluding non-significant determinants ($p > 0.05$) in order to create the final multivariate model.

RESULTS

A total of 440 individuals (Table I) were included in the present study and completed lung function and respiratory muscle strength measurements.

Lung function

Predicted values of lung function (FVC, FEV_1, PEF) for any individual with SCI who meets the inclusion criteria of this study can be calculated using the regression equations shown in Table II. Prediction values of respiratory muscle strength (Pi_{max} and

Table I. *Participants' characteristics*

	Tetraplegia		Paraplegia		
Group	High	Low	High	Low	Total
Gender, M/F, *n*	89/17	95/28	90/22	77/22	351/89
TPI, years, median [2.5–97.5%]	8.5 [0.6–33.3]	8.5 [0.8–40.6]	6.6 [0.7–46.1]	6.4 [0.7–44.1]	15.7, 0.7–40.9]
Age, years, median [2.5–97.5%]	43 [21–69]	46 [22–71]	49 [22–73]	45 [21–76]	47, 21–72]
Height, cm, median [2.5–97.5%]	178 [158–195]	175 [160–195]	176 [153–192]	176 [156–196]	175, 157–194]
Body mass, kg, median [2.5–97.5%]	73 [44–95]	72 [50–109]	75 [40–106]	74 [50–108]	74, 49–106]

TPI: time post-injury.

Table II. *Regression coefficients (βi values) and 95% confidence intervals (CI) from the multivariate multilevel. Regression analysis of lung function parameters*

	FVC (l) β [95% CI]	FEV_1 (l) β [95% CI]	PEF (l/s) β [95% CI]
Constant	–1.219 [0.569 to –3.007]	–0.798 [0.692 to –2.288]	–1.327 [2.025 to –4.679]
ΔHT–LT	–0.599* [–0.387 to –0.811]	–0.531* [–0.357 to –0.705]	–1.105* [–0.733 to –1.477]
ΔLT–HP	0.371* [0.583 to 0.159]	0.280* [0.458 to 0.102]	0.902* [1.316 to 0.488]
ΔLT–LP	0.791* [1.013 to 0.570]	0.608* [0.794 to 0.422]	1.725* [2.203 to 1.247]
Gender	0.645* [0.868 to 0.422]	0.505* [0.691 to 0.318]	1.049* [1.467 to 0.632]
Age (years)	–0.026* [–0.020 to –0.032]	–0.025* [–0.021 to –0.029]	–0.031* [–0.021 to –0.041]
Height (cm)	0.024* [0.034 to 0.014]	0.021* [0.029 to 0.013]	0.032* [0.052 to 0.012]
Body mass (kg)	0.010* [0.016 to 0.004]	0.006* [0.010 to 0.002]	0.015* [0.025 to 0.005]
TPI (years)	n.s.	n.s.	n.s.

*Significant influencing factor ($p<0.05$); n.s.: not significant.
FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 s; PEF: peak expiratory flow; β: regression coefficient for each independent variable; CI: confidence interval; HT: high tetraplegia; LT: low tetraplegia; HP: high paraplegia; LP: low paraplegia; ΔHT–LT/ΔLT–HP/ΔLT–LP: group dummies with LT as reference; gender: 0: women; 1: men; TPI: time post-injury.

Pe_{max}) can be calculated using the regression equations shown in Table III. The calculation of the predicted FVC of, for example, a male individual with a T2 lesion, 37 years old, 178 cm tall with a body mass of 72 kg would be as follows:

FVC = –1.219 (*constant*) + 0.371 (*HP group*) + 0.645 (*male*) + (37*–0.026) (*age*) + (178*0.024) (*height*) + (72*0.010) (*body mass*) = 3.83 litres.

Group means of FVC, FEV_1 and PEF values increased with lower lesion level, but showed a large range between individuals of the same group (Fig. 1). The 95% confidence intervals (95% CI) shown in Table II further support the finding that there can be some variability among the predicted values. Multivariate analysis showed that all tested lung function parameters are significantly associated with the level of injury. In general, individuals with lower lesion levels showed higher values than individuals with higher lesion levels. Men showed significantly higher values than women, younger individuals showed higher values than older ones, taller and heavier individuals showed higher values than smaller and lighter ones. TPI and the interaction of lesion level and age had no significant influence on any of the tested lung function parameters. R^2 for FVC was 0.55, for FEV_1 0.52 and for PEF 0.40, which indicates the part of the variance that can be explained by the factors included in the model.

Table III. R*egression coefficients (βi values) and 95% confidence intervals (CI) from the multivariate multilevel regression analysis of respiratory muscle strength parameters*

	Pi_{max} (cmH_2O) β [95% CI]	Pe_{max} (cmH_2O) β [95% CI]
Constant	45.31 [62.48; 28.14]	55.72 [68.70; 42.75]
ΔHT–LT	–11.98* [–4.38; –19.59]	–7.87 [1.71; –17.45]
ΔLT–HP	10.90 [19.52; 2.28]	9.09 [17.77; 0.41]
ΔLT–LP	19.89* [30.96; 8.82]	36.18* [48.70; 23.66]
Gender	14.95* [22.87; 7.03]	19.74* [28.11; 11.37]
Age (years)	–0.60* [–0.38; –0.82]	–0.52* [–0.17; –0.87]
Height (cm)	n.s.	n.s.
Body mass (kg)	0.51* [0.73; 0.29]	n.s.
TPI (years)	n.s.	0.46* [0.75; 0.17]

*Significant influencing factor ($p<0.05$); n.s.: not significant.
Pi_{max}: maximal inspiratory pressure; Pe_{max}: maximal expiratory pressure; β: regression coefficient for each independent variable; CI: confidence interval; HT: high tetraplegia; LT: low tetraplegia; HP: high paraplegia; LP: low paraplegia; ΔHT–LT/ΔLT–HP/ΔLT–LP: group dummies with LT as reference; gender: 0: women; 1: men; TPI: time post-injury.

Maximal respiratory muscle strength

Predicted values of respiratory muscle strength (Pi_{max} and Pe_{max}) for any individual with SCI who meets the inclusion criteria of this study can be calculated using the regression equations shown in Table III. Similarly to lung function parameters, the group means of Pi_{max} and Pe_{max} increased with lower lesion level, but also showed a large range between individuals of the same group (Fig. 2), and this is further supported by the large CIs shown in Table III. Pi_{max} and Pe_{max} were significantly associated with the level of lesion as well as with gender. Individuals with lower lesion levels showed higher values than those with higher lesion levels, and men showed higher

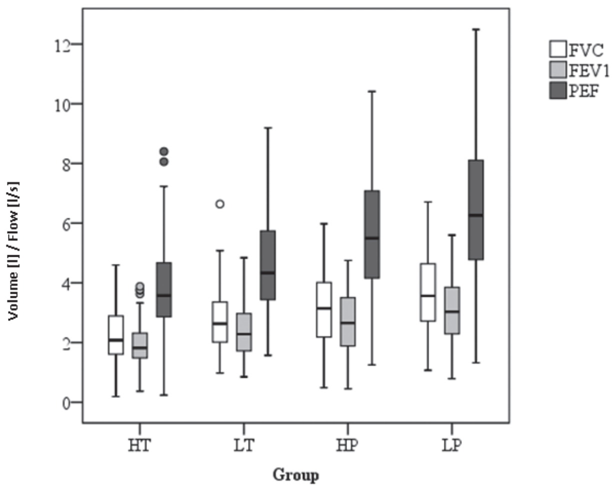

Fig. 1. Boxplots for forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1) and peak expiratory flow (PEF) given for the 4 lesion-level subgroups. HT: individuals with high tetraplegia (C4, C5); LT: individuals with low tetraplegia (C6–C8); HP: individuals with high paraplegia (T1–T6); LP: individuals with low paraplegia (T7–T12); °: outlier.

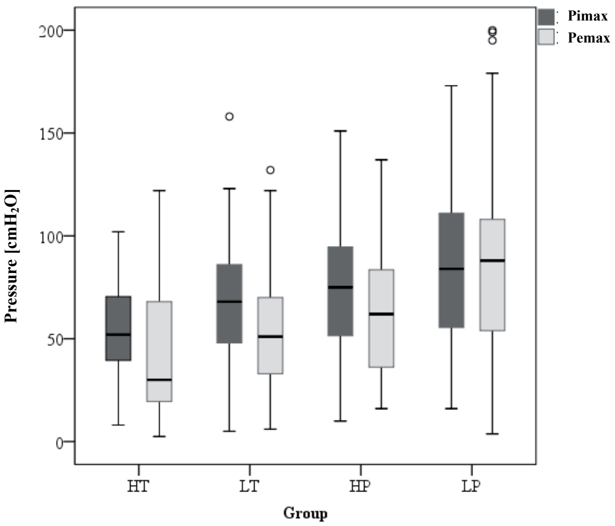

Fig. 2. Boxplots for maximal inspiratory pressure (Pi_{max}) and maximal expiratory pressure (Pe_{max}) given for the 4 lesion-level subgroups. HT: individuals with high tetraplegia (C4, C5); LT: individuals with low tetraplegia (C6–C8); HP: individuals with high paraplegia (T1–T6); LP: individuals with low paraplegia (T7–T12); °: outlier.

values than women. Increasing age had a negative influence on Pi_{max} and Pe_{max}, whereas greater body mass was positively associated with Pi_{max} but not with Pe_{max}. Height and TPI had no significant influence on Pi_{max}. Pe_{max} was positively associated with TPI. The interaction of lesion level and age had no significant influence on Pi_{max} and Pe_{max} and therefore was not included in the final models. The total variance of the models that can be explained by included factors (R^2), was 0.37 for Pi_{max} and 0.46 for Pe_{max}.

DISCUSSION

Summary of the main findings

Lung function and respiratory muscle strength of persons with SCI are influenced by similar parameters as in able-bodied persons (15, 18), such as gender, age and height, but additionally by body mass and lesion level. Interestingly, Pe_{max} is the only parameter that is influenced by TPI. In addition, the open-access webpage (www.scionn.nl/RefCalc.xls) has been created in order to make it easy to calculate reference values for individuals with motor complete SCI. The system automatically calculates the predicted lung function or respiratory strength value from the personal and lesion characteristics of the individual. Furthermore, if measured values of the actual individual are entered, the percentage of the predicted value for this particular individual will be calculated. Instructions on how to use the tool are included on the website.

Lung function

The regression coefficients of the parameter "age" in the present study are all between –0.025 and –0.031 (Table II), representing a decrease in lung function of between 25 and 31 ml or ml/s for each year. Interestingly, these coefficients for persons with motor complete SCI are in accordance with those for able-bodied persons, who lose between 26 and 43 ml or ml/s for each year (19). There was no additional decrease in lung function with increasing TPI.

Coughing ability is an important function for prevention of respiratory complications, especially pneumonia. It has been shown that FEV_1 does not correlate with the clearance efficacy of coughing (20). PEF may be more closely associated with coughing than FVC and FEV_1. In order to produce an effective cough, a PEF of 5–6 l/s is necessary (21). The mean PEF of persons with tetraplegia in the present study was approximately 4–5 l/s, indicating that these persons are not able to produce an effective cough and therefore may be at higher risk for respiratory complications. Thus, PEF could be a useful screening parameter in persons with SCI, in order to detect risk factors for respiratory complications early on. The fact that body mass positively influences lung function seems confusing, since it is known that being overweight decreases lung function in the able-bodied population (22). Nevertheless, our sample of individuals was not overweight (Table I), having a mean body mass index (BMI) of 23.9 kg/m^2. Jones et al. (23) showed that vital capacity is negatively influenced mainly in persons with a BMI of > 30 kg/m^2.

Respiratory muscle strength

Similar to regression equations for lung function, a lower lesion level had significant positive effects on Pi_{max} and Pe_{max}. Similar to in able-bodied individuals and the models for lung function, gender showed significant effects on Pe_{max} and Pi_{max}, with higher estimates for men than women. Similarly to reference equations for able-bodied persons (18), increasing age had a significant negative effect on respiratory muscle strength in persons with SCI. Interestingly, Pe_{max} was positively associated with TPI. This is an unexpected result that may have been influenced by selection bias. In an earlier study we showed that Pe_{max} increases in individuals with tetraplegia at least until 2 years post-injury (24). However, the increase in Pe_{max} with increasing TPI in the present study may result from selection of individuals with good respiratory function, i.e. those who survived.

Clinical relevance

This is the first study investigating parameters influencing lung function and respiratory muscle strength in a large cohort of motor complete individuals with SCI. Our data showed that, compared with able-bodied persons, other parameters such as lesion level and body mass are important parameters influencing respiratory function in individuals with SCI. Detailed knowledge of these parameters may help to optimize respiratory care management in daily clinical practice in the future because respiratory complications in individuals with tetraplegia are common and are still the major cause of death (3). First studies show that respiratory muscle training may improve respiratory function (25–27), but further studies with larger sample sizes and of high methodological quality are necessary (28, 29).

Furthermore, the easy to use open-access tool supports physicians in estimating individual predicted lung function and respiratory muscle strength values from personal and lesion-level data. Since innervation of respiratory muscles is highly influenced by the lesion level, this has to be considered for calculating reference values of lung function for persons with SCI. The results provided by our newly designed reference values calculator give a rapid general overview of the current lung function status of an individual with SCI and should therefore improve the individual and long-term respiratory care of persons with SCI.

Study limitations

Respiratory complications occur frequently in persons with SCI (30, 31) and seem to be associated with low respiratory function (5, 6). This study provides further knowledge of respiratory function in persons with SCI. However, it cannot provide any information about risk of respiratory complications resulting from a decrease in respiratory function. To evaluate this important question, longitudinal studies assessing respiratory function and complication rates are needed.

Smoking may be an additional influencing parameter on lung function values. Since we only had smoking data from the 8 Dutch centres, we could not include this parameter in our models. However, we analysed the Dutch sub-set of data to test any influence of smoking on the measured parameters of respiratory function. Interestingly we found no significant effect of smoking or the number of pack-years on any of the tested parameters.

Examining the R^2 values for the 5 models assessed indicates that only 37–55% of the variability in respiratory function values can be explained by the parameters included in our models. The large CIs shown in Tables II and III further show that there may be some variability in the predicted values, which should be taken into account when interpreting calculated and measured values. This makes clear that other factors, such as physical fitness, respiratory muscle training, medication or smoking, may further influence respiratory function parameters. Nevertheless, we believe that it is at least a clinically relevant starting point to be able to explain 37–55% of the variability. Including these proportions in interpretation of the data shows that it is worth measuring lung function and respiratory muscle strength, but assessing additional potentially influencing factors that are not included in our models (see above) may help the clinician to explain why a patient is above or below the reference value and may improve individuals' respiratory care.

A further limitation of this study is the lack of validation of our models. We tested our models with a dozen individuals, and the values were quite accurate. However, a new study with prognostic models, including more potentially influencing factors, is necessary for a proper validation of these models. We plan to test another 400–500 individuals in a subsequent multi-centre cohort study in order to validate the models presented in this paper.

Conclusion

Lesion level has a significant influence on lung function and respiratory muscle strength in persons with SCI. Lesion level should therefore be considered carefully when assessing respiratory function in persons with SCI. Using the regression equations presented in this study may be helpful for calculating "reference-like" data to compare lung function of persons with SCI. Persons with motor complete tetraplegia should be screened regularly by testing lung function and respiratory muscle strength with the aim of preventing respiratory complications.

ACKNOWLEDGEMENTS

The Dutch part of this study was supported by the Dutch Health Research and Development Council, ZON-MW Rehabilitation programme, grant number 1435.0003.

The contribution of the 9 participating rehabilitation centres, in particular that of the research assistants collecting all the data, is highly appreciated: Sacha van Langeveld (De Hoogstraat, Utrecht), Annelieke Niezen/Peter Luthart (Rehabilitation Center Amsterdam), Marijke Schuitemaker (Het Roessingh, Enschede), Karin Postma (Rijndam Revalidatiecentrum, Rotterdam), Jos Bloemen (Hoensbroeck Revalidatiecentrum, Hoensbroeck), Hennie Rijken (Sint Maartenskliniek, Nijmegen), Ferry Woldring (Beatrixoord, Haren), Linda Valent (Heliomare, Wijk aan Zee) and Claudia Muri (Swiss Paraplegic Center, Nottwil). We thank Jörg Krebs for critically reading the manuscript.

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